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REEVES, J

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892. 2 pages
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449. 1 page
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-9 are pending in the application.
   Of the above, claims 5-6 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-4, 7-9 are rejected.
5. ☐ Claims _____ are objected to.
6. ☑ Claims 1-9 are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 1-4 and 7-9, drawn to an anti-idiotype antibody which contains an internal image of the ganglioside GD2 antigen, classified in Class 424, subclasses 131.1 and 178.1.

Group II. Claims 5-6, drawn to a method of treatment, classified in Class 424, subclass 131.1 and Class 436, subclass 501.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case the antibody product can be used for other uses, including diagnostic methods, than the treatment method claimed in Invention II. Therefore, Inventions I and II are patentably distinct.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Demetra Mills on July 13, 1995 a provisional election was made with traverse to prosecute the invention of I, claims 1-4 and 7-9. Affirmation of this election must be made by applicant in responding to this Office action. Claims 5-6 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

6.This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

7. The disclosure is objected to because of the following informalities: on page 4, line 3, the reference for **Chatterjee** et al in Volume 150 of the **FASEB Journal** (1993) is confusing, as the FASEB Journal has not published a Volume 150 in 1993. However, an abstract of **Bhattacharya-Chatterjee** et al has been located in Volume 150 of the **Journal of Immunology** (1993)(S). Applicant is required to clarify the inconsistency or otherwise to provide a copy of the reference cited in the specification.

On page 11, lines 17-21, in the sentence "In previous studies of the inventors, **small animals**, such as mice and rabbits, after three to four times immunization bi-weekly with anti-Id 1A7 coupled to KLH and mixed with Freund's Adjuvant, **induced anti-GD2 antibodies**" it is not clear whether the small animals induced the antibody response or whether the process of immunization induced the antibody response. Applicant is required to appropriately amend the specifications to clarify the sentence cited on page 11, lines 17-21.

On page 18, lines 14-15, the phrase "50 ul of **different concentration** of PRO#685 or PRO#778 (Aba) **was added**", it is not clear that if the applicant meant to recite that **a different concentration was added** and if so, different from what, or if the applicant meant to recite that **different concentrations were added**. Applicant is required to amend the specifications in order to clarify what the applicant meant to recite.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. In particular, the specification fail to describe the adequately identity and source for the anti-GD2 antibody (Ab1), as demonstrated in the examples set forth below:

On page 11, lines 7-9, the applicant recites the "anti-idiotype antibody 1A7, raised against a **known** anti-GD2 antibody (14G2a)

[that] mimics GD2 antigen". However, the applicant does not provide a reference or source for this "known" antibody.

On page 11, lines 15-17, the applicant recites that the murine monoclonal anti-Id 1A7 was raised against anti-GD2 mAb 14G2a (isotype IgG2a-k) obtained from **Scripps**, La Jolla. It is not clear that the term **Scripps** refers to the **Scripps Institute** and, if so, from which laboratory within the Scripps Institute the monoclonal anti-GD2 antibody was obtained.

Further, on page 11, lines 22-25, the applicant recites that "a **murine monoclonal antibody mAb (IgG2ak)** which binds to the ganglioside GD2 in human melanoma, neuroblastoma, glioma and sarcoma **has been used to generate monoclonal antibodies (Ab2)** in BALB/c mice". It is not clear that this anti-GD2 antibody is the same **14G2a** antibody as recited in lines 15-17 and lines 29-32. Moreover, it is uncertain that this anti-GD2 antibody is Ab1 nor is it clear from which source the **murine monoclonal antibody** was obtained. In the absence of knowledge of what antibody (Ab1) was used to generate Ab2, one of ordinary skill in the art would not be able to reproduce the claimed antibody without undue experimentation.

9. The specification is objected to under 35 USC § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological material.

The specification lacks complete deposit information for the deposits of the hybridoma producing the monoclonal antibody designated 1A7. Because it is not clear that anti-idiotypic antibodies possessing the properties of 1A7, particularly having the internal image of GD2 and being capable of generating active immunity to melanoma, are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because best mode disclosed by the specification requires the use of the 1A7 monoclonal antibody, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible production of the cell lines and antibodies claimed, or filing of evidence of deposits commensurate in scope with the claims is required. Without a publicly available deposit of the cell line, one skilled in the art could not be assured of the ability to practice the invention claimed. Note that the best mode is not satisfied by a written disclosure unless the exact embodiment is reasonably reproducible from that disclosure. If

reproducibility of the cell line is not established, failure to deposit the cell line would result in concealment of the best mode contemplated by applicant for carrying out the invention. In re Sherwood, 615F.2d 809, 204 U.S.P.Q. 537 (CCPA 1980).

Applicant's "Statement of Deposit" set forth at pages 10-11 of the specification is noted. **However**, it is noted that the specification and the claims refer to the deposit of the monoclonal antibody 1A7 and **not** the **hybridoma** producing the 1A7. Monoclonal antibodies are not deposited microorganisms. The Statement of Deposit would be deemed sufficient to satisfy the requirements of 37 CFR 1.801-1.809 if Applicant were to amend the specification and the claims to indicate that "the hybridoma producing the monoclonal antibody 1A7" has been deposited as ATCC Accession No. HB-11786.

Applicant's attention is directed to 37 C.F.R. §§ 1.801-1.809, M.P.E.P. §§ 2402-2411.05 and In re Lundak, 773 F.2d. 1216, 227 U.S.P.Q. 90 (CAFC 1985) for further information concerning the Rules and Regulations for the Deposit of Biological Materials for Patent Purposes.

Claims 1-4 and 7-9 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

10. The specification is objected to under 35 USC § 112, first paragraph, for failing to provide an enabling disclosure commensurate in scope with the claimed subject matter. The Applicant claims that the anti-idiotype monoclonal antibody can be used as a substitute for GD2 antigen in biochemical or serological assays. From the specification, there is not evidence for the use the of 1A7 as a substitute for the GD2 antigen in biochemical or serological assays. Nor is it apparent that the antibody 1A7 could be used as a substitute, for example, for GD2 in an assay that measured GD2 activity. It is not clear that 1A7 would be able to substitute in a functionally equivalent manner for the GD2 in any biochemical or serological assays due to the differences in molecular weights, chemical compositions and physical properties of immunoglobulins and sphingolipids. Without such disclosure, one of ordinary skill in the art would not be able to practice the claimed invention with a reasonable expectation of success and without undue experimentation.

11. Claims 7-8 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

12. The specifications fail to enable the diagnostic test kit recited in claim 9. Applicant has provided no evidence that the 1A7 antibodies can bind to patient's sera nor that there are antigen in the patient's sera that are capable of binding to the 1A7 monoclonal antibody. Applicant has failed to provide sufficient evidence for use of the 1A7 antibody to generate the data necessary to correlate with the detection of melanoma and small cell carcinomas as recited in claim 9 with 1A7 antibody/antigen binding. From the examples set forth in the specification, it is not clear that the 1A7 antibody will bind to the GD2 antigen in the presence of sera proteins. Seaver (R) discloses that "selection of the final antibodies [for clinical diagnosis] requires work with **real clinical specimens**" to ensure selection of a monoclonal antibody that has high sensitivity and specificity necessary for clinical diagnosis (see fourth column, first full paragraph). In the absence of such evidence, one of ordinary skill in the art would not be able to make or use the claimed invention with a reasonable expectation of success and without undue experimentation.

13. Claim 9 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

14. Applicant is reminded that when amending the specification, 35 U.S.C. 132 prohibits the addition of **new matter** in the specification.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bhattacharya-Chatterlee et al (S). The claims recite an anti-idiotype antibody 1A7 that is an internal image of the GD2 ganglioside antigen. The claims also recite that the antibody generates an active immunity to GD2 antigen which is highly expressed on malignant melanoma cell and small cell carcinoma.

Bhattacharya-Chatterlee et al disclosed that "a murine mAb 14G2a which binds to the ganglioside GD2... has been used to generate monoclonal anti-Id Ab2 in syngeneic BALB/c mice". Further, the

abstract states that "one of these clones, 1A1-1A7 has been used to raise anti-anti-Id antibodies (Ab3) in rabbits". The prior art goes on to teach that "the polyclonal rabbit Ab3 sera competed with Ab1 for binding". Thus, the 1A1-1A7 antibody of the prior art appears to be identical to the 1A7 antibody claimed by applicant. Both were raised by immunization of mice with the anti-GD2 antibody 14G2a, both are paratopes in that they complete with the GD2 antigen binding site and both have been shown to be capable of generating active immunity. It is the examiner's position that Bhattacharya-Chatterlee et al have already fully disclosed to the public an anti-idiotype mAb 1A7 that generates an active immunity to GD2 antigen which is found on melanoma and small cell carcinomas. Further as disclosure of the anti-Id antibody 1A7 and its immunogenicity in rabbits occurred more then one year prior to Applicant's application date, issuance of a patent is barred.

17. Claims 1-3 are rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Saleh et al (T). Saleh et al teach the "generation of a human anti-idiotype antibody that mimics the GD2 antigen" (see title) by immunization with the murine mAb 14G2a (see page 3391, first column, third and fourth full paragraphs). Moreover, prior art recites the use of a "murine monoclonal anti-GD2

Antibody 14G2a" that was "produced by Abbott Laboratories and provided by the Biological Response Modifier Program of the National Cancer Institute (IND BB3159)" (see page 4342, title and second column, second full paragraph). Further, the authors disclose "the ability of this human anti-Id to generate both a humoral and cellular anti-GD2 immune response" (see page 3396, first column, first full paragraph). Therefore, it is the Examiner's position that Saleh et al have produced an anti-Id antibody 4B5 that is directed to the same antigen as the Applicants' 1A7 and that this antibody has the same properties as that of Applicants' 1A7 in that it can be used to generate active immunity to GD2. One of ordinary skill in the art would reasonably conclude that Saleh's antibody also possesses the internal image of the GD2 ganglioside and, therefore, it appears that Saleh et al have produced an antibody that is identical to the Applicants' 1A7. Since the Patent and Trademark Office does not have the facilities for examining and comparing Applicants' 1A7 antibody with the antibody of Saleh et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed 1A7 and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197).

18. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

19. Claims 1-4 and 7-9 are rejected under 35 U.S.C. § 103 as being unpatentable over Mujoo et al (U) in view of Cheung et al (V). Mujoo et al disclose the anti-GD2 monoclonal antibody 14G2a that is identical to the Applicants' immunogen but do not teach the use of this antibody to create anti-idiotypic antibodies. Cheung et al have produced 6 anti-idiotype rat monoclonal antibodies that compete with the GD2 antigen and induce the production of anti-GD2 antibodies upon immunization into mice. Further, Cheung et al disclose that one would want to make anti-idiotypic antibodies to the GD2 antibody as "the disialoganglioside GD2 is widely expressed among neuroblastomas,

melanomas, small-cell carcinomas, sarcomas and brain tumors. Since GD2 is poorly immunogenic, anti-idiotypic antibodies may serve as alternative tumor vaccines" (see abstract). However, Cheung et al do not disclose the use of the GD2 antibody 14G2a. In view of Cheung et al's success with their anti-idiotypic antibodies, one of ordinary skill in the art at the time the invention was made would have sufficient motivation and a reasonable expectation of success to use the readily available 14G2a monoclonal antibody from Mujoo et al to produce anti-idiotypic antibodies that would generate active immunity against malignant melanomas and small-cell carcinomas, as demonstrated by Cheung et al. Further, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the anti-idiotype antibodies in combination with a pharmacologically acceptable carrier, such as phosphate buffered saline solution, or conjugated to a detectable label such as the ones set forth in claim 8. Such methods are well known and conventional in the art. Further, it would have been obvious to one skilled in the art at the time the invention was made to package the monoclonal antibody for use as a diagnostic test kit as a convenience for sale in the marketplace.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie

Reeves whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr, can be reached on (703) 308-2454. The fax phone number for this Group is (703) 305-7362.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Julie Reeves

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ROBERT D. BUDENS
PRIMARY EXAMINER
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